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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,874	02/06/2001	Iris Pecker	01/21603	8407

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	11

DATE MAILED: 10/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/776,874	Applicant(s) PECKER ET AL.	
	Examiner Richard G Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 June 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants preliminary amendment canceling claims 1-13 and adding new claims 14-65, Paper No. 6, 5/2/2001, is acknowledged. Claims 14-65 are at issue and are present for examination.

Election/Restrictions

Applicant's election of Group I, in Paper No. 9 is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

The drawings are objected to for the reasons stated on the form PTO-948.

Specification

The disclosure is objected to because of the following informalities:

Figures 1, 16, 17, and 19 each contain amino acid or nucleic acid sequences, but do not list a corresponding sequence identifier in the figure or in the description of the figure. See M.P.E.P.

> **2422.02** The Requirement for Exclusive Conformance; Sequences Presented in Drawing Figures
> ... It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings.

Appropriate correction is required.

Claim Objections

Claims 44-53 are objected to because of the following informalities:

Claims 44-53 each recite "...having a pair of glutamic acids participating in its active site...". It is suggested that applicants amend this to "...having a pair of glutamic acid **residues** participating in its active site...".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-23, 30-33, 40-43, 50-53 and 60-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20-23, 30-33, 40-43, 50-53 and 60-63 are indefinite in that they each recite or depend from a claim that recites "...insect cell derived sugar prosthetic groups..." (claims 20, 21, 30, 31, 40, 41, 50, 51 60 and 61) or "...non-human cell derived sugar prosthetic groups..." (claims 22, 23, 32, 33, 42, 43, 52, 53, 62, and 63) which is confusing. It is unclear what a "prosthetic group" is, and therefore what makes such a "prosthetic group" from insects different from human, different from non-humans?

Claims 18, 19, 28, 29, 38, 39, 48, 49, 58 and 59 are indefinite in that the recitations "CXC chemokine" and "PAI1" are unclear. What is encompassed by each of these terms?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-33, and 44-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14-33, and 44-65 are directed to all possible preparations comprising a protein having heparanase catalytic activity or being cleavable so as to acquire said heparanase catalytic activity, and pharmaceutical compositions comprising said preparation, wherein said preparation is free of non-heparanase polypeptides encoded by human nucleic acid sequences" (claims 14, 15, 24, 24, 44, 45, 54 and 55), wherein said isolated protein is substantially devoid of glycosilation (claims 16, 17, 26, 27, 46, 47, 56 and 57), wherein the preparation is substantially free of a CXC chemokine or PAI1 (claims 18, 19, 28, 29, 48, 49, 58 and 59), wherein said isolated protein is characterized by insect cell derived sugar prosthetic groups (claims 20, 21, 30, 31, 50, 51 60 and 61), wherein said isolated protein is characterized by non-human cell derived sugar prosthetic groups (claims 22, 23, 32, 33, 52, 53, 62, and 63).

The specification, however, only provides a single representative species isolated of such preparations and pharmaceutical compositions comprising said preparation wherein the protein having heparanase catalytic activity has the amino acid sequence of SEQ ID NOs: 10, 14 or 44, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these preparations, compositions or proteins by any identifying structural characteristics or properties other than the activities recited in claims, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed

invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 14-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants amendment to claims 14-63 which recite "the preparation being free of non-heparanase polypeptides encoded by human nucleic acid sequences" (claims 14, 15, 24, 24, 34, 35, 44, 45, 54 and 55), "... said isolated protein being substantially devoid of glycosilation..." (claims 16, 17, 26, 27, 36, 37, 46, 47, 56 and 57), "...the preparation being substantially free of a CXC chemokine or PAI1" (claims 18, 19, 28, 29, 38, 39, 48, 49, 58 and 59), "...said isolated protein characterized by insect cell derived sugar prosthetic groups..." (claims 20, 21, 30, 31, 40, 41, 50, 51 60 and 61), or "...said isolated protein characterized by non-human cell derived sugar prosthetic groups..." (claims 22, 23, 32, 33, 42, 43, 52, 53, 62, and 63), are not supported by the original disclosure and therefore considered new matter.

Claims 14-33, and 44-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein or preparation comprising said protein at least 90% homologous to SEQ ID NO: 10, said protein having heparanase activity or being so cleavable so as to acquire said heparanase activity, does not reasonably provide enablement for any protein or preparation comprising said protein having heparanase activity or being so cleavable so as to acquire said heparanase activity, regardless of whether said protein is about 50 or about 65 kDa, has a pair of glutamic acids participating in its active site, or capable of eliciting anti-heparanase antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 14-33, and 44-65 are so broad as to encompass any protein or preparation comprising said protein having heparanase catalytic activity or being cleavable so as to acquire said heparanase catalytic activity, and pharmaceutical compositions comprising said preparation, wherein said protein or preparation is free of

non-heparanase polypeptides encoded by human nucleic acid sequences" (claims 14, 15, 24, 24, 44, 45, 54 and 55), wherein said isolated protein is substantially devoid of glycosilation (claims 16, 17, 26, 27, 46, 47, 56 and 57), wherein the preparation is substantially free of a CXC chemokine or PAI1 (claims 18, 19, 28, 29, 48, 49, 58 and 59), wherein said isolated protein is characterized by insect cell derived sugar prosthetic groups (claims 20, 21, 30, 31, 50, 51 60 and 61), wherein said isolated protein is characterized by non-human cell derived sugar prosthetic groups (claims 22, 23, 32, 33, 52, 53, 62, and 63).

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins, preparations and pharmaceutical compositions comprising said preparations, broadly encompassed by the claims, including all proteins or preparation comprising said proteins wherein said protein has heparanase activity or is so cleavable so as to acquire said heparanase activity. The claims rejected under this section of U.S.C. 112, first paragraph, do not place minor if any structural limits on the claimed protein. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is

limited to that protein and preparation comprising said protein wherein said protein has the amino acid sequence of SEQ ID NO: 10, 14 or 44.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any protein having heparanase catalytic activity because the specification does not establish: (A) regions of the protein structure which may be modified without effecting heparanase catalytic activity; (B) the general tolerance of heparanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a heparanase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the heparanase catalytic activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood

and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those proteins of the claimed genus having the claimed heparanase catalytic activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any heparanase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Fuks et al. (U.S. Patent No. 5,362,641).

Fuks et al. disclose a heparanase derived the human SK-HEP-1 Cell line, useful for the stimulation of wound healing. Fuks et al. further teach the use of this purified heparanase and formulations containing the same in therapies such as for the stimulation and enhancement of wound healing. The heparanase of Fuks et al. is the same protein as that of the instant application and capable of eliciting an anti-heparanase antibody and therefore Fuks et al. anticipates claims 64 and 65.

Claims 14-17, 22-23, 54-57 and 62-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoogwerf et al. (WO 95/04158).

Hoogwerf et al. teach a large number of cDNAs and vectors and host cells comprising said cDNAs, which encode proteins with heparanase activity as well as the proteins themselves. The recombinant proteins taught by Hoogwerf et al. have heparanase activity, are free of non-heparanase polypeptides encoded by human nucleic acid sequences, substantially devoid of glycosilation, characterized by noon-human cell derived sugar groups and are capable of eliciting an anti-heparanase antibody Hoogwerf et al. additionally teach the use of the purified heparanase for therapeutic wound healing by the administration of a pharmaceutical composition comprising the purified heparanase.

Therefore, Hoogwerf et al. anticipates claims 14-17, 22-23, 54-57 and 62-65.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-63 are rejected under 35 U.S.C. 103(a) as obvious over Fuks et al. (U.S. Patent No: 5,362,641).

Fuks et al. disclose a heparanase derived from the human SK-HEP-1 Cell line, useful for the stimulation of wound healing. Fuks et al. further teach the use of this purified heparanase and formulations containing the same in therapies such as for the stimulation and enhancement of wound healing. The heparanase of Fuks et al. is the same protein as that of the instant application, having a molecular weight of about 50 kDa, comprising the amino acid sequence of SEQ ID NO: 10 and having a pair of glutamic acid residues participating in its active site.

One of ordinary skill in the art at the time of filing would have been motivated to isolate the cDNA that encodes the heparanase taught by Fuks et al. and express this cDNA in an expression system utilizing either bacteria, yeast or insect cells. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Said recombinantly produced heparanase proteins could be isolated such that they are

free of non-heparanase polypeptides encoded by human nucleic acid sequences. Such proteins isolated from *E. coli* would be substantially devoid of glycosilation, substantially free of a CXC chemokine or PAI1," (claims 18, 19, 28, 29, 38, 39, 48, 49, 58 and 59). Such proteins isolated from insect cells would be characterized by insect cell derived sugar groups and therefore characterized by non-human cell derived sugar groups. Therefore, Fuks et al. makes obvious claims 14-63.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
October 18, 2002

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.